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Effects of terlipressin on patients with sepsis via improving tissue blood flow

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ABSTRACT

Terlipressin (TP), an analog of arginine vasopressin, was reported beneficial in sepsis patients when combined use with norepinephrine (NE), but the undetermined action, mechanism, and safety limited it to become the first-line vasopressor for sepsis patients. With 32 septic shock patients, we investigated the effects of a small dose of TP (1.3 μg/kg/h) on hemodynamic, tissue blood flow, vital organ function, acid–base balance, and coagulation function to systemically know the beneficial effect and side effects of TP on septic shock. The results showed that as compared with the single use of NE group (17 patients), a small dose of TP (1.3 μg/kg/h) in combination with NE continuous infusion, except for decreasing the mortality and NE requirement, could better improve and stabilize the hemodynamics, improve the tissue blood flow, increase the blood oxygen saturation and urine volume, and decrease the lactate level and complication rate (47% *versus* 82.3% in NE group). Meanwhile, TP + NE did not induce blood bilirubin increase and platelet count decrease and hyponatremia that vasopressin has. The results show that low dose of TP continuous infusion can help NE achieve the good resuscitation effect by improving tissue blood flow, stabilizing hemodynamics, and protecting organ function in septic shock patients while did not induce the side effects that high dose or bonus of TP or vasopressin induced. Low dose of TP may be recommended as the first-line vasopressor for refractory hypotension after severe sepsis or septic shock.

1. Background and rational

With its fast onset, high mortality, and difficulty for treatment, severe sepsis and septic shock are severe problems in the intensive care unit (ICU). They are the main reasons for the death of hospitalized ICU patients with noncoronary heart disease [1]. The annual mortality of sepsis and septic shock is ≈150,000 in Europe and 225,000 in the United States [2]. The morbidity is ≈2.9% among all hospitalized patients and 10% in ICU patients [3]. The mortality of severe sepsis and septic shock among ICU patients is as high as 32.2% and 54.1%, respectively [4].

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Effective treatments for septic shock at early stage include circulation, respiratory, and metabolic support as well as antibiotic application except for the treatment of infectious sources. Among these measures, effective fluid resuscitation and hemodynamic support (especially achievement of the "6-h resuscitation goal") are the key measures for successful treatment of severe sepsis and septic shock. The central object is stabilizing hemodynamics and increasing the tissue perfusion. However, the present success rate to achieve this goal is only 52% [5–8].

The major obstacles preventing from achieving the early resuscitation goal for severe sepsis and septic shock are resistance to vasoactive agents (insensitivity or no response). This is called "vascular hyporeactivity", the major reason causing refractory hypotension in these patients [9,10]. Arginine vasopressin (AVP) has been demonstrated effective and recommended as the first-line vasopressor in vasodilatory and refractory shock after sepsis [11,12]. However, many studies have demonstrated that AVP has no specificity for V1 and V2 receptors (1:1). Hence, AVP, except for having modulatory effect on vascular reactivity via V1 receptor, can often induce the decrease of cardiac output and platelet (PLT) count, increase the blood direct and indirect bilirubin (DBIL and IBIL) level, and induce hyponatremia and water retention via V2 receptors [13–16]. Terlipressin (TP), an analog of AVP, has stronger binding specificity for the V1 receptor than AVP (2.2:1 for the V1 receptor:V2 receptor) [17–19]. It has stronger vascular contraction activity in sepsis-induced refractory hypotension. Some studies including meta-analysis showed TP could decrease the mortality and requirement of norepinephrine (NE) in patients with sepsis and septic shock [20]. However, the mechanism responsible for the beneficial effect of TP and the side effects are not clear. Some studies showed that TP at large doses or bonus administration can decrease the cardiac output, induce hyponatremia and water retention, and affect coagulation function and bilirubin metabolism [21–23]. The unclear mechanism and safety (without enough evidences) and limited clinical trials restricted TP to be recommended as the first-line vasopressor for sepsis patients.

To elucidate this issue, with 32 septic shock patients, we further investigated the beneficial effect of a small dose of TP continuous infusion (1.3 μg/kg/h) for septic shock patients, investigated if TP obtained beneficial effect via increasing the tissue perfusion and organ function, and investigated the related side effects. It is aimed to provide more evidences and usage principal for TP for more clinical application in sepsis.

2. Materials and methods

2.1. Ethical approval of the study protocol

The study protocol was approved by the Ethics Committee of the Research Institute of Surgery at Daping Hospital of the Third Military Medical University (Chongqing, China). The clinical trial was registered in the International Clinical Trial Registration Center (ChiCTR-TRC-11,001,583). All participants provided their written informed consent or from their close relatives to participate in this study.

2.2. Diagnostic criteria of septic shock and primary end point of this trial

Experiments were conducted in the central ICU of Daping Hospital, Chongqing, China. The basic information of patients was collected from patients' families. Experiment was carried out from March 2011–March 2013. The diagnosis criteria for sepsis are core temperature ≥38°C or ≤36°C, heart rate (HR) ≥90 b/min, respiratory rate ≥20 c/min, or the use of mechanical ventilation for an acute respiratory process, leukocyte count ≥12,000/mm^3 or ≤4000/mm^3, or differential count showing >10% immature neutrophils [5]. The diagnostic criteria for septic shock were systolic blood pressure (SBP) <90 mm Hg, mean arterial blood pressure (MAP) <65 mm Hg (or SBP decreased by 40 mm Hg as compared with basic blood pressure), and no effect for fluid resuscitation using 20–40 mL/kg crystalloid solution [24]. The primary end point was to achieve the early resuscitation goals (within 6 h after administration of TP) including (1) central venous pressure (CVP) 8–12 mm Hg, (2) 65 mm Hg ≤MAP ≤90 mm Hg, (3) urine volume ≥0.5 mL/kg/h, and (4) central venous saturation of oxygen ($ScvO_2$; superior vena cava) ≥70%. The minor end point was to achieve tissue blood flow and organ function improvement after administration of TP.

2.3. The inclusion and exclusion criteria and trial protocol

The inclusion criteria of patients in this trial included (1) ICU patients existing sepsis; (2) with refractory hypotension (SBP <90 mm Hg, MAP <65 mm Hg); and (3) vasoactives must be given to maintain the MAP ≥65 mm Hg after adequate fluid resuscitation. The exclusion criteria in this trial included (1) age <18 y; (2) complicated with left ventricular dysfunction (cardiac index <2.2 L/min/m^2 when pulmonary wedge pressure >18 mm Hg); (3) with coronary heart disease; (4) with apparent valvular heart disease; and (5) presence (or suspected) of ischemia in the mesenteric arteries or vascular spasm diseases. Thirty-two patients whose MAP <65 mm Hg after adequate fluid resuscitation and a continuous infusion of NE (the dosage was >0.5 μg/min/kg) was needed to keep MAP ≥65 mm Hg were randomized and blindly into sole NE group (17 patients) and NE + TP group (15 patients).

Patients in the NE group received enough fluid plus intravenous infusion of NE to maintain the MAP ≥65 mm Hg but ≤95 mm Hg. Patients in the NE + TP group received enough fluid plus intravenous infusion of NE and a small dose of TP (1.3 μg/kg/h) to maintain MAP ≥65 mm Hg [3–5]. All patients received anesthesia (fentanyl and midazolam) and ventilator-assisted control breathing. The breathing mode was volume-controlled ventilation. According to the 2008 international sepsis treatment guidelines [23], except for fluid resuscitation, NE and NE + TP, the basic treatment measures including organ protection and antibiotics, and so on for each patient in the two groups were similar. All participants provided their written informed consent or from their close relatives to participate in this clinical trial.